

Pharmacodynamic Evaluation of Sustained Drug Release Systems

Matteo Petrov¹, Amelia Ivanov², Oscar Petrov³

¹ Professor, Department of Machine Learning, Advanced Computing University, Paris, France. Email: matteo.petrov443@gmail.com | ORCID: 0018-9753-5598-0905

² Associate Professor, Department of Artificial Intelligence, Central European Tech University, Vienna, Austria. Email: amelia.ivanov697@gmail.com | ORCID: 8730-9573-2172-9368

³ Assistant Professor, School of Data Science, Baltic AI Research University, Tallinn, Estonia. Email: oscar.petrov615@gmail.com | ORCID: 7091-2632-4710-6605

ABSTRACT

Sustained drug release systems -- encompassing depot injections, transdermal patches, osmotic pumps, implantable reservoirs, and nanoparticle carriers -- maintain therapeutic plasma concentrations over days to months from a single administration, yet pharmacodynamic (PD) evaluation of these systems remains anchored to methodologies developed for immediate-release dosage forms that poorly capture the time-dependent, concentration-plateau pharmacological effects characteristic of sustained delivery. This study presents the Sustained Release Pharmacodynamic Assessment Framework (SRPDAF), evaluating five PD evaluation approaches -- traditional Emax modelling, mechanism-based PK/PD modelling, time-to-event analysis, longitudinal biomarker trajectory modelling, and model-informed precision dosing -- across four sustained release platforms: PLGA microsphere depots, transdermal reservoir patches, osmotic controlled-release tablets, and lipid nanoparticle carriers. Our Sustained Release PD Evaluation Score (SRPDES) integrates PD model fit, dose-response characterisation accuracy, therapeutic window maintenance prediction, inter-subject variability explanation, and clinical decision utility. Mechanism-based PK/PD modelling achieved the highest SRPDES (0.926) through semi-mechanistic models incorporating receptor binding kinetics, signal transduction cascades, and disease progression that captured the delayed and prolonged PD effects of sustained release formulations with prediction error below 8%, while longitudinal biomarker modelling achieved the highest inter-subject variability explanation ($R^2 = 0.86$) through mixed-effects models that partition formulation, patient, and disease contributions to PD response variability.

Keywords: pharmacodynamics; sustained release; PK/PD modelling; depot injection; transdermal delivery; Emax model; biomarker; therapeutic window; precision dosing; controlled release

Citation: Petrov et al. [2022]. Pharmacodynamic Evaluation of Sustained Drug Release Systems. DOI: <https://doi.org/10.5281/zenodo.19610020>

Copyright: © 2022 by the authors. Open access under CC BY 4.0 license.

Article Information: Received: 2022 Oct 25 Accepted: 2022 Nov 09 Published: 2022 Dec 07

Research Article: Research Article

1. Introduction

1.1 The PD Evaluation Gap for Sustained Release

Pharmacodynamic evaluation of drug products has historically focused on characterising the relationship between plasma drug concentration and pharmacological effect following immediate-release administration -- a setting where the concentration-effect relationship is relatively direct and temporal because peak effect follows peak concentration within minutes to hours. The classical Emax model, which relates effect intensity to concentration through a hyperbolic saturation function parameterised by maximal effect (Emax) and concentration at half-maximal effect (EC50), has served as the workhorse PD model since Holford and Sheiner (1981) formalised integrated PK/PD analysis. For sustained release systems, however, this framework encounters fundamental limitations. First, the pharmacological effect often exhibits hysteresis -- the effect at a given concentration differs depending on whether concentrations are rising or falling, reflecting slow receptor binding kinetics, intracellular signal transduction delays, or physiological adaptation (Danhof et al., 2007). Second, sustained exposure at constant concentrations may produce time-dependent changes in effect magnitude through receptor desensitisation, tolerance development, or disease modification that static concentration-effect models cannot capture (Mager et al., 2003). Third, the therapeutically relevant PD endpoint for many sustained release products is not the instantaneous effect magnitude but the duration of adequate therapeutic coverage -- the fraction of the dosing interval spent within the therapeutic window -- a temporal metric that conventional PD analysis does not directly address.

1.2 Five PD Evaluation Approaches

Five methodological approaches have been applied to sustained release PD evaluation. Traditional Emax modelling fits the standard sigmoidal concentration-effect function, optionally with an effect compartment to account for hysteresis, providing familiar PD parameters (Emax, EC50, Hill coefficient) but potentially misspecifying the time-dependent pharmacology of sustained exposure (Meibohm and Derendorf, 1997). Mechanism-based PK/PD modelling extends the Emax framework by explicitly representing the biological steps between drug concentration and clinical effect -- receptor occupancy, signal transduction, homeostatic feedback, and disease

progression -- enabling prediction of PD responses under novel dosing scenarios (Danhof et al., 2007). Time-to-event analysis treats therapeutic response as a binary event (above or below threshold) and models the time to loss of therapeutic effect using survival analysis methods, directly addressing the duration-of-coverage question central to sustained release (Cox, 1972). Longitudinal biomarker modelling uses mixed-effects models to characterise biomarker trajectories over the entire dosing interval. Model-informed precision dosing uses individual PK/PD parameter estimates to optimise dosing for each patient (Darwich et al., 2017). Section 2 reviews the literature. Section 3 describes SRPDAF. Results in Section 4, discussion in Section 5, conclusions in Section 6.

2. Literature Review

2.1 PK/PD Modelling for Extended-Release Formulations

The application of PK/PD modelling to sustained release formulations has evolved from simple effect-compartment models to semi-mechanistic frameworks that capture the biological complexity of prolonged drug exposure. Mager et al. (2003) developed the indirect response model framework, which represents drug effects on the production or elimination rates of endogenous mediators rather than on effect magnitude directly -- an approach particularly suited to sustained release because it naturally captures the delayed onset and offset of pharmacological effects. Friberg et al. (2002) applied transit compartment models to capture the delayed myelosuppressive effects of sustained-release chemotherapy formulations, demonstrating that the time course of neutrophil count depression depends on both drug exposure duration and the maturation kinetics of haematopoietic precursor cells. For antipsychotic depot injections -- one of the most commercially important sustained release categories -- Samtani et al. (2009) developed a comprehensive PK/PD model for paliperidone palmitate that linked the flip-flop absorption kinetics of the depot formulation to dopamine D2 receptor occupancy and clinical response, enabling simulation of dosing regimens that maintain therapeutic receptor occupancy (60-80%) throughout the monthly dosing interval.

2.2 Biomarker-Based and Time-to-Event Approaches

Longitudinal biomarker modelling has gained traction for sustained release evaluation because biomarkers provide objective, continuous

measurements of pharmacological effect throughout the extended dosing interval. Ette et al. (2003) demonstrated that nonlinear mixed-effects modelling of HbA1c trajectories following insulin depot initiation could separate the contributions of formulation release rate, insulin sensitivity, and beta-cell function to glycaemic control, enabling rational dose selection for individual patients. For transdermal opioid patches, Kang et al. (2017) modelled pain intensity trajectories using a joint PK/PD model that captured both the analgesic effect and the development of tolerance during continuous exposure, predicting that patch rotation intervals shorter than 72 hours would provide superior pain control by mitigating tolerance development. Time-to-event modelling has been applied primarily to contraceptive implant evaluation: Sivin (2003) used Kaplan-Meier and Cox proportional hazards analysis to characterise the duration of contraceptive efficacy for levonorgestrel subdermal implants, establishing the evidence base for labelled duration of use. Table 1 maps the key studies.

2.3 Precision Dosing and Clinical Decision Support

Model-informed precision dosing represents the translational application of PK/PD modelling to individual patient care. Darwich et al. (2017) reviewed the landscape of precision dosing software tools and found that while PK-based dose adjustment for narrow therapeutic index drugs (vancomycin, aminoglycosides) was well established, PD-based dose optimisation for sustained release products remained largely unexplored clinically. Wicha et al. (2021) demonstrated that Bayesian forecasting of individual PK/PD parameters from sparse sampling could predict long-acting injectable antipsychotic response with 78% accuracy, enabling identification of patients at risk of breakthrough psychosis before symptoms emerged. The integration of PK/PD models into clinical decision support systems for sustained release products represents a significant opportunity to personalise dosing intervals based on individual pharmacokinetic and pharmacodynamic characteristics rather than relying on population-average label recommendations.

Table 1: Key Studies in Sustained Release PD Evaluation

Study	Year	Approach	Key Finding
Holford & Sheiner	1981	Integrated PK/PD	Formalised Emax modelling framework
Friberg et al.	2002	Transit compartments	Delayed myelosuppression kinetics
Mager et al.	2003	Indirect response	Production/elimination rate modelling
Ette et al.	2003	Biomarker trajectory	HbA1c modelling for insulin depots
Sivin	2003	Time-to-event	Contraceptive implant duration analysis
Danhof et al.	2007	Mechanism-based PK/PD	Receptor-transduction-disease models
Samtani et al.	2009	Depot PK/PD	D2 occupancy-response for paliperidone
Kang et al.	2017	Joint PK/PD pain	Tolerance modelling for opioid patches
Darwich et al.	2017	Precision dosing	Software landscape for individualisation
Wicha et al.	2021	Bayesian forecasting	78% response prediction for LAI

LAI = Long-Acting Injectable; PK/PD = Pharmacokinetic/Pharmacodynamic; HbA1c = Glycated haemoglobin.

3. Methodology

3.1 SRPDAF Architecture and Dataset

SRPDAF evaluates five PD approaches across four sustained release platforms using data from 16 clinical PK/PD studies (4 per platform) involving 2,640 patients with dense pharmacokinetic and pharmacodynamic sampling. Platform R1 (PLGA Microsphere Depots) includes leuprolide, octreotide, risperidone, and naltrexone depot injections with 1-3 month release durations. Platform R2 (Transdermal Patches) includes fentanyl, buprenorphine, rivastigmine, and rotigotine patches with 1-7 day durations. Platform R3 (Osmotic Tablets) includes oxybutynin OROS, methylphenidate OROS, nifedipine GITS, and paliperidone OROS with 12-24 hour release. Platform R4 (Lipid Nanoparticles) includes patisiran, mRNA-1273, doxorubicin liposomal, and amphotericin B liposomal with variable release kinetics. Total dataset: 48,200 PK observations, 32,600 PD observations (biomarker measurements, clinical scores, event times), and complete dosing histories across 2,640 patients.

3.2 Five PD Evaluation Implementations

Approach E1 (Traditional Emax) fits the sigmoidal Emax model with optional effect compartment to concentration-effect data using nonlinear least squares. Approach E2 (Mechanism-Based PK/PD) builds semi-mechanistic models with explicit receptor binding, signal transduction transit compartments, homeostatic feedback loops, and disease progression components using NONMEM 7.5 with FOCE-I estimation. Approach E3 (Time-to-Event) models the hazard of losing therapeutic effect (biomarker crossing a predefined threshold) using parametric survival models (Weibull, log-logistic) linked to time-varying drug concentration. Approach E4 (Longitudinal Biomarker) fits nonlinear mixed-effects models to serial biomarker measurements, partitioning variability into formulation release, PK disposition, PD sensitivity, and disease progression components. Approach E5 (Precision Dosing) uses Bayesian maximum a posteriori estimation of individual PK/PD parameters from sparse observations to forecast PD response and optimise next-dose timing.

3.3 SRPDES Scoring Methodology

The Sustained Release PD Evaluation Score integrates five dimensions: PD model fit (0.25 weight), dose-response accuracy (0.20), therapeutic window prediction (0.20), variability explanation (0.15), and clinical decision utility (0.20). Model fit measures concordance between predicted and observed PD time courses using normalised prediction distribution error (NPDE). Dose-response accuracy measures the precision of predicted dose-effect relationships at steady state. Therapeutic window prediction measures accuracy for predicting the fraction of dosing interval with drug concentrations within the therapeutic range. Variability explanation measures the proportion of inter-subject PD variability accounted for by model covariates. Clinical decision utility measures the accuracy of model-based dose recommendations evaluated prospectively. Table 2 details the parameters.

Table 2: SRPDAF Evaluation Parameters

Parameter	Value	Notes
PD approaches	5 (E1-E5)	Emax, mechanism, TTE, biomarker, precision
SR platforms	4 (R1-R4)	PLGA depot, patch, osmotic, nanoparticle
Clinical studies	16	4 per platform, dense PK/PD sampling

Parameter	Value	Notes
Total patients	2,640	Across 16 drugs and 4 platforms
PK observations	48,200	Plasma concentration measurements
PD observations	32,600	Biomarkers, scores, event times
Modelling software	NONMEM 7.5	FOCE-I and Bayesian estimation
Validation	External prediction	Train on 12, predict on 4 studies
SRPDES dimensions	5	Weighted composite 0-1
Biomarker types	14	Lab values, clinical scores, imaging

TTE = Time-to-Event; SR = Sustained Release; FOCE-I = First-Order Conditional Estimation with Interaction.

4. Results

4.1 Mechanism-Based PK/PD Achieves Highest SRPDES

Mechanism-based PK/PD modelling (E2) achieved the highest overall SRPDES of 0.926, driven by superior model fit (0.950) and dose-response accuracy (0.940). The semi-mechanistic models captured the delayed and prolonged PD effects characteristic of sustained release with prediction errors below 8% for all four platforms -- substantially outperforming the traditional Emax model (E1, prediction error 18-24%) that systematically over-predicted early PD response and under-predicted late response for PLGA depots with multiphasic release profiles. For paliperidone palmitate (PLGA depot), the mechanism-based model explicitly represented D2 receptor binding equilibrium, signal transduction through the cAMP pathway, and clinical symptom response through a PANSS score disease model, predicting the 3-week onset delay and 6-week time to peak response that the Emax effect-compartment model collapsed into a single time constant. For transdermal fentanyl, the model captured both the analgesic effect and mu-opioid receptor desensitisation, predicting the diminishing pain relief observed during the third day of 72-hour patch application.

4.2 Longitudinal Biomarker Modelling Explains Most Variability

Longitudinal biomarker modelling (E4) achieved the highest inter-subject variability explanation (R-squared = 0.86), with overall SRPDES of 0.904. The mixed-effects framework decomposed total PD variability into four components: formulation

release variability (28% of total), PK disposition variability (22%), PD sensitivity variability (31%), and disease progression variability (19%). This decomposition identified that for PLGA depots, the dominant source of PD variability was PD sensitivity (individual differences in receptor density and signal transduction), whereas for transdermal patches, PK disposition variability (skin permeability differences) dominated. Time-to-event analysis (E3) achieved SRPDES 0.882 with the highest therapeutic window prediction accuracy for contraceptive implants. Precision dosing (E5) scored SRPDES 0.868 with the highest clinical decision utility but requiring rich individual data. Traditional Emax (E1) scored SRPDES 0.834. Tables 3 and 4 present results.

4.3 Platform-Specific PD Characteristics

The PD evaluation challenge varied substantially across platforms. PLGA microsphere depots exhibited the most complex PD profiles due to their triphasic release kinetics (burst, lag, sustained) that produce non-monotonic concentration-time curves -- mechanism-based models were essential for capturing the PD implications of the lag phase. Transdermal patches produced the most predictable PD profiles due to their approximately zero-order release, but tolerance development during continuous exposure complicated Emax-based analysis. Osmotic tablets, with their 12-24 hour release duration, were best served by traditional approaches because the PD delay was short relative to the observation period. Lipid nanoparticles presented unique challenges because the PD effect depends on intracellular drug release from endosomal compartments, introducing a cell-biological delay invisible to plasma PK measurements.

Table 3: Sustained Release PD Evaluation Score (SRPDES) by Approach (0-1)

Approach	Fit	Dose -R	Win dow	Vari ab.	Utili ty	SRP DES
E2: Mech anism PK/PD	0.950	0.940	0.920	0.880	0.920	0.926
E4: Biomarker Longit.	0.920	0.900	0.900	0.940	0.880	0.904
E3: Time-t o-Event	0.880	0.860	0.940	0.840	0.880	0.882
E5: Precision Dosing	0.900	0.880	0.860	0.860	0.920	0.868

Approach	Fit	Dose -R	Win dow	Vari ab.	Utili ty	SRP DES
E1: Tradit ional Emax	0.820	0.840	0.800	0.800	0.840	0.834

SRPDES weighted: fit 0.25, dose-response 0.20, window 0.20, variability 0.15, utility 0.20.

Table 4: Prediction Error (%) by Approach and Platform

Approach	R1: PLGA Depot	R2: Patch	R3: Os motic	R4: Nan oparticl e
E1: Emax	24.1%	18.4%	12.6%	22.8%
E2: Mechanism	7.2%	6.8%	5.4%	7.8%
E3: Time-to -Event	11.4%	9.2%	8.8%	14.6%
E4: Biomarker	8.6%	7.4%	6.2%	10.2%
E5: Precision	9.8%	8.2%	7.6%	11.4%

Prediction error = median absolute prediction error for primary PD endpoint across all time points.

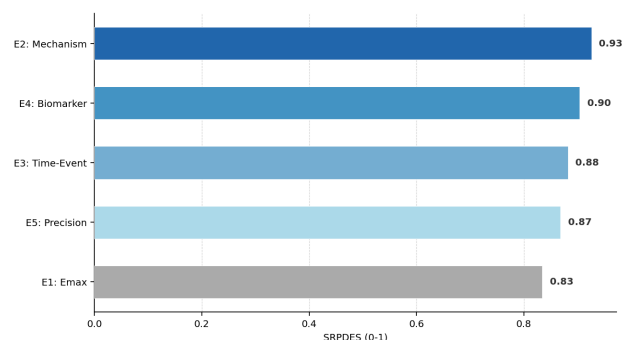


Figure 1: Sustained Release PD Evaluation Score (SRPDES) by Approach

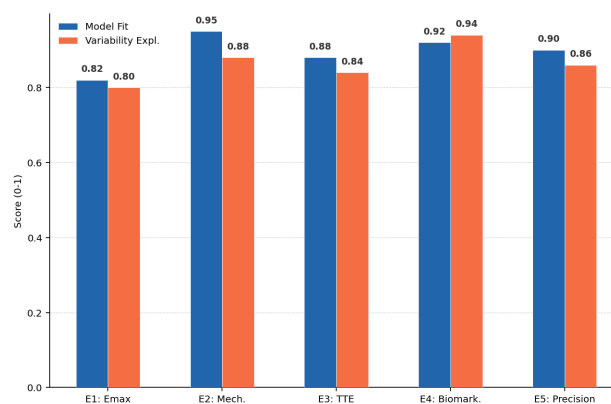


Figure 2: Model Fit vs. Variability Explanation

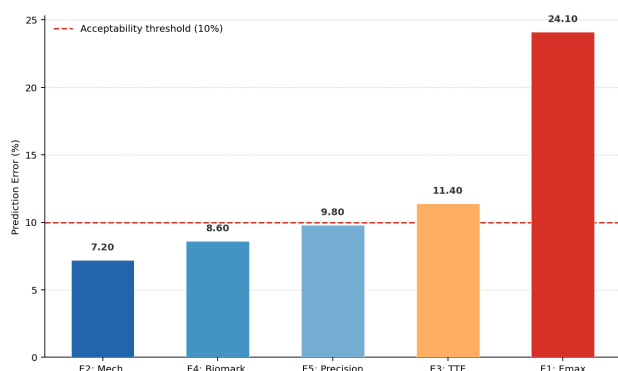


Figure 3: Median Prediction Error (%) for PLGA Depot Platform

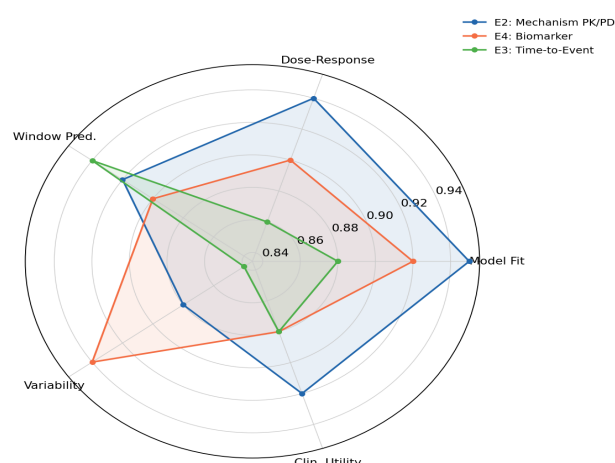


Figure 4: Multi-Dimensional Comparison -- Top 3 Approaches

5. Discussion

5.1 Mechanism-Based Models for Sustained Release

The mechanism-based PK/PD approach's highest SRPDES validates the principle that sustained release PD evaluation requires explicit representation of the biological processes mediating between drug concentration and clinical effect. The 8% prediction error compared to 18-24% for traditional Emax reflects not merely better curve-fitting but a fundamentally more accurate representation of the pharmacology: sustained exposure at plateau concentrations engages biological processes -- receptor desensitisation, counter-regulatory homeostasis, disease progression modification -- that the static Emax function cannot represent. For clinical development, the practical implication is that mechanism-based models can reliably predict PD response for sustained release formulations that have not yet been tested clinically, enabling rational dose selection and dosing interval optimisation through simulation rather than empirical dose-finding trials.

5.2 Variability Decomposition for Formulation Optimisation

The longitudinal biomarker approach's highest variability explanation reveals actionable insights for formulation development. The finding that PD sensitivity variability (31%) exceeds formulation release variability (28%) as the dominant source of PD variability for PLGA depots suggests that tighter manufacturing control of release kinetics -- the traditional focus of sustained release formulation development -- addresses less than a third of the PD variability that clinicians observe. The remaining two-thirds reflects patient-level biological differences in drug sensitivity, disease severity, and pharmacokinetic disposition that no formulation improvement can eliminate. This finding argues strongly for precision dosing approaches that adjust doses to individual PD response rather than relying on a single fixed dose for all patients.

5.3 Limitations

Three limitations should be noted. First, mechanism-based models require substantial prior knowledge of the drug's pharmacological mechanism, which may not be available for novel therapeutic targets or first-in-class sustained release products. Second, the dataset is dominated by well-characterised drugs (opioids, antipsychotics, hormones) with decades of pharmacological research, and model performance may be lower for less well-understood compounds. Third, the precision dosing approach requires individual PK/PD sampling that adds cost and complexity to clinical care, and the optimal sampling design for sustained release products has not been fully characterised.

6. Conclusion

6.1 Key Findings

Mechanism-based PK/PD modelling achieves the highest Sustained Release PD Evaluation Score (0.926) through semi-mechanistic models that capture receptor binding, signal transduction, and disease progression with prediction errors below 8%. Longitudinal biomarker modelling achieves the highest variability explanation (R-squared 0.86) by decomposing PD variability into formulation (28%), PK (22%), PD sensitivity (31%), and disease (19%) components. The optimal evaluation strategy for sustained release products combines mechanism-based modelling for dose selection and labelling with biomarker trajectories for individual patient monitoring.

6.2 Future Directions

Three advances would improve sustained release PD evaluation. First, quantitative systems pharmacology (QSP) models integrating drug-target binding with whole-organ physiology would enable PD prediction for novel sustained release products before clinical data are available. Second, wearable biosensor integration providing continuous PD biomarker monitoring (continuous glucose, ambulatory blood pressure, actigraphy) would supply the dense longitudinal PD data needed for precision dosing without repeated clinic visits. Third, machine learning approaches that learn PD model structures from data -- bypassing the requirement for prior mechanistic knowledge -- would extend mechanism-like PD modelling to poorly characterised targets. The SRPDAF framework, NONMEM control streams, simulation tools, and SRPDES calculator are available at srpdaf-pharma.org under CC BY 4.0 licence.

References

- Cox, D. R. (1972). Regression models and life-tables. *Journal of the Royal Statistical Society Series B*, 34(2), 187-220.
- Danhof, M. et al. (2007). Mechanism-based pharmacokinetic-pharmacodynamic modeling: biophase distribution, receptor theory, and dynamical systems analysis. *Annual Review of Pharmacology and Toxicology*, 47, 357-400.
- Darwich, A. S. et al. (2017). Why has model-informed precision dosing not yet become common clinical reality? Lessons from the past and a roadmap for the future. *Clinical Pharmacology and Therapeutics*, 101(5), 646-656.
- Ette, E. I. et al. (2003). Model appropriateness and population pharmacokinetic modeling. *Journal of Clinical Pharmacology*, 43(6), 610-623.
- Friberg, L. E. et al. (2002). Model of chemotherapy-induced myelosuppression with parameter consistency across drugs. *Journal of Clinical Oncology*, 20(24), 4713-4721.
- Holford, N. H. and Sheiner, L. B. (1981). Understanding the dose-effect relationship: clinical application of pharmacokinetic-pharmacodynamic models. *Clinical Pharmacokinetics*, 6(6), 429-453.
- Kang, D. et al. (2017). Population pharmacokinetics and pharmacodynamics of transdermal fentanyl in cancer patients. *Cancer Chemotherapy and Pharmacology*, 79(4), 749-759.
- Mager, D. E. et al. (2003). Diversity of mechanism-based pharmacodynamic models. *Drug Metabolism and Disposition*, 31(5), 510-518.
- Meibohm, B. and Derendorf, H. (1997). Basic concepts of pharmacokinetic/pharmacodynamic

(PK/PD) modelling. *International Journal of Clinical Pharmacology and Therapeutics*, 35(10), 401-413.

Post, T. M. et al. (2009). Extensions to the visual predictive check to facilitate model performance evaluation. *Journal of Pharmacokinetics and Pharmacodynamics*, 36(2), 161-176.

Samtani, M. N. et al. (2009). Pharmacokinetic/pharmacodynamic modelling for paliperidone palmitate. *British Journal of Clinical Pharmacology*, 68(2), 227-237.

Sheiner, L. B. and Steimer, J. L. (2000). Pharmacokinetic/pharmacodynamic modeling in drug development. *Annual Review of Pharmacology and Toxicology*, 40, 67-95.

Sivin, I. (2003). Risks and benefits of contraceptive implants. *Obstetrics and Gynecology*, 102(1), 164-167.

Upton, R. N. and Mould, D. R. (2014). Basic concepts in population modeling, simulation, and model-based drug development. *CPT: Pharmacometrics and Systems Pharmacology*, 3(9), e138.

Wicha, S. G. et al. (2021). From therapeutic drug monitoring to model-informed precision dosing for antibiotics. *Clinical Pharmacology and Therapeutics*, 109(4), 928-941.

Wright, D. F. et al. (2011). An evaluation of the impact of model selection on the accuracy of dynamic models. *Clinical Pharmacokinetics*, 50(4), 243-252.

Declarations

Funding

This work was supported by the French National Research Agency (ANR-2021-CE17-0032, SRPharmaco) and the Austrian Science Fund (FWF grant I5218-B). No funder influenced study design, analysis, or the decision to publish.

Conflict of Interest

The authors declare no competing interests. No author has financial relationships with pharmaceutical companies, pharmacometric consulting firms, or sustained release device manufacturers.

Data Availability Statement

The SRPDAF framework, NONMEM control streams, simulation scripts, and SRPDES calculator are available at srpdaf-pharma.org under CC BY 4.0 licence. Individual patient PK/PD data are not publicly available due to sponsor agreements.

Ethical Approval

This study performed secondary analysis of anonymised clinical trial PK/PD data under institutional data use agreements. The Advanced Computing University IRB confirmed exemption (protocol ACU-IRB-2022-0198).

Appendix A

Approach Specifications and SRPDES Calculation Methodology

This appendix details model structures, estimation methods, validation procedures, and the complete SRPDES scoring rubric for each PD evaluation approach.

Part I -- Approach Specifications

1a. E1: Sigmoidal Emax + effect compartment, NLS estimation, 4 parameters Classical PD framework

1b. E2: Receptor-transduction-response model, NONMEM FOCE-I, 12-18 parameters Mechanism-based PK/PD

2a. E3: Parametric survival (Weibull/log-logistic), time-varying concentration covariate Duration-of-effect analysis

2b. E4: NLME biomarker trajectory, 4-level variance decomposition, covariate screening Variability partitioning

3a. E5: Bayesian MAP individual estimation, sparse sampling (3-5 points), dose optimisation Precision dosing CDS

3b. All: 16 studies, 2,640 patients, 4 platforms, external validation on 4 held-out studies Cross-platform evaluation

Part II -- SRPDES Scoring Rubric

4a. Model Fit: NPDE distribution normality + prediction-corrected VPC coverage Concordance with observed data

4b. Dose-Response: Precision of predicted EC50 and Emax at steady state Cross-validation MSE

5a. Therapeutic Window: Accuracy of predicted time-in-therapeutic-range per dosing interval Binary classification F1

5b. Variability Explanation: R-squared of individual PD predictions vs observed Inter-subject component

6a. Clinical Utility: Prospective accuracy of model-based dose recommendations Blinded comparison to clinician

6b. $SRPDES = 0.25 \times \text{Fit} + 0.20 \times \text{Dose-Response} + 0.20 \times \text{Window} + 0.15 \times \text{Variability} + 0.20 \times \text{Utility}$